REMARKS

This Reply is responsive to the Office Action dated April 23, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.116 is respectfully requested.

The application has been amended as set forth above. In accordance for the new rules for amending applications set forth in 37 CFR 1.121, which took effect on March 1, 2001, a marked up version of the claims showing all amendments is attached hereto as an appendix.

Claim 1 has been amended in accordance with the language already approved in U.S. Patent No. 6,011,138 ('138) in order to clarify the nature of the claimed antibodies. In particular, claim 1 has been amended to clarify that the claimed antibodies inhibit IL-4 induced expression in vitro to a greater extent than the antibody lacking a gamma-1 or gamma-3 constant region. Claims 6 and 7 were canceled because the limitations recited therein were incorporated into claim 1. Claims 16, 19, 20, 38 and 39 were canceled because the claims on which they depend were canceled.

The '138 patent issued from application No. 08/803,085, which is the parent application to the present application. During prosecution of the application for the '138 patent, all the references cited by the present Examiner were considered and dismissed as irrelevant to claims issued therein, which are directed to an anti-human CD23 antibody having human gamma-1 constant regions wherein said antibody inhibits IgE expression to a greater extent than the antibody lacking gamma-1 constant regions. For instance, see the front page of the '138 patent and the prosecution file history.

The present application was filed to expand the scope of protection to include gamma-3 antibodies, given the observation that the Fc receptors that bind to gamma-1 constant regions also bind gamma-3 (see discussion in specification at page 15, lines 18-25). Because the present inventors have discovered that effector function plays an important role in the inhibition of IgE expression using CD23 antibodies, and that gamma-1 constant regions mediate this effector function, it is logical given the similar binding characteristics of gamma-1 and gamma-3 that anti-CD23 antibodies containing gamma-3 domains will also be successful at inhibiting IgE antigen-specific responses.

The newly amended claims are similar to those issued in the '138 patent except that they encompass antibodies with either a gamma-1 or gamma-3 constant region domain. Thus, any prior art challenge that is made will in effect challenge the validity of an issued

patent unless it is pertinent to gamma-3 antibodies alone. Prior art rejections that do not concern gamma-3 antibodies alone but that extend to gamma-1 antibodies should require the permission of the Group Director in that such rejections amount to a challenge of a valid U.S. patent. Indeed, the presumption of patent validity created by section 282 of the Patent Act reflects a respect for the PTO's technical knowledge and expertise in determining when the conditions for patentability have been satisfied. Sidewinder, 597 F.2d at 205, 202 USPQ at 361; Chicago Rawhide Manufacturing Co. v. Crane Packing Co., 523 F.2d 452, 457-58, 187 USPQ 540, 545 (7th Cir. 1975), cert. denied, 423 U.S. 1091, 188 USPQ 480 (1976).

Turning then to the Office Action, claims 1, 2, 4-9 and 14-22 were rejected under 35 U.S.C. §102(a) as being allegedly anticipated by Bonnefoy (WO 96/12741) as evidenced by Saxon et al (1991, J. Immunol. Vol. 147(11): 4000-06). According to the Examiner, Bonnefoy teaches anti-CD23 antibodies that have a human IgG1 or IgG3 constant region whether or not such antibodies were actually made, and Saxon et al evidence that such antibodies inherently inhibit IgE expression. Applicants respectfully traverse this rejection.

First, it is noted that claim 1 has been amended to incorporate the language of claim 1 issued in the '138 patent. Again, applicants respectfully note that both Bonnefoy and Saxon were considered and dismissed during prosecution of the '138 patent (see the references cited on the face of the patent). Thus, claim 1 as amended is not anticipated by the cited references because the only difference between claim 1 in the present application and claim 1 in the '138 patent is that the present claim 1 expands the scope of the claim to also include such anti-CD23 antibodies having human gamma-3 constant regions. Such human gamma-3 antibodies would be expected to mediate the same effector related functions as human gamma-1 antibodies because they bind to the same Fc receptors.

Indeed, while Bonnefoy includes a laundry list of human constant region domains in the disclosure of WO 96/12741, and states that any of such constant regions may be employed in either rat or mouse chimeric or humanized antibodies disclosed therein, Bonnefoy does not exemplify or describe any specific chimeric or humanized antibody. Furthermore, Bonnefoy certainly does not teach a chimeric or humanized antibody that inhibits IgE expression by B cells to a greater extent than the same antibody without such constant regions. Rather, Bonnefoy only teaches that such antibodies may elicit a lesser immune response (see page 5 of Bonnefoy, lines 8-11).

Moreover, Bonnefoy's prophetic mention of chimeric and humanized antibodies is made amidst a laundry list of binding agents including complete antibodies, $F(ab')_2$

fragments, Fab fragments, Fv fragments, ScFv fragments, "other" fragments, CDR peptides, mimetics, recombinant antibodies, chimaeric antibodies, humanized antibodies, primatized antibodies, antibody-toxin fusion proteins, etc. There is no guidance for the skilled artisan to pick any one of these types of modified antibodies let alone a subtype of one of these types in order to identify an antibody that inhibits IgE expression to a greater extent than the others. In this regard, the CCPA has held that where a reference patent's generic disclosure encompasses a vast number of species and subspecies, even though applicants' claimed compounds are encompassed by the broad generic disclosure, the disclosure by itself does not describe applicants' claimed invention within the meaning of 35 U.S.C. §102. See In re Petering, 133 USPQ 275 (CCPA 1962).

Thus, Applicants respectfully submit that Bonnefoy does not anticipate the claimed invention because Bonnefoy gives no direction to the skilled artisan reading his disclosure as to which of the species or subspecies in the lengthy laundry list of different antibody types will achieve increased inhibition of IgE expression. Applicants particularly fail to see where Bonnefoy expressly teaches antibodies having a primate antigen binding portion as recited in claim 2. Bonnefoy does mention that primatizing techniques may be used at page 6, lines 1-2; however, given that Bonnefoy also states at the line just prior to that that variable regions are either rat or mouse variable regions, it is reasonable to presume that Bonnefoy referred to primatizing techniques as incorporation of a primate constant region, not a primate variable region. Thus, Bonnefoy is clearly not §102 art as to claim 2.

Regarding the rejection of claim 1 and the other remaining claims, applicants respectfully maintain their position that Bonnefoy is more appropriately applied as a §103(a) reference, in which case the evidence of unexpected results is probative of patentability. In response, the Examiner appears to challenge the surprising and unexpected nature of the results on page 3 of the Office Action where she states that the primate antibody 6G5 and the primatized versions having gamma-1 and gamma-4 constant regions, respectively, performed "the same at all three concentrations of antibody in the inhibition of IL-4-induced IgE expression, noting the standard error bars." The Examiner further alleges that the 5E8 primatized antibodies with the gamma-1 human constant region "perform comparably" to the 5E8 primatized antibodies with the gamma-4 human constant region, noting the standard error bars. Applicants respectfully but strenuously disagree.

Regarding 6G5, Figure 5 clearly shows that the gamma-1 version (6G5G1) performs better (inhibits IgE expression to a greater extent) than the gamma-4 version (6G5G4P). This

distinction is most apparent at the highest concentration tested (3 μg/ml) where the gamma-1 version completely inhibited IgE production. However, the distinction is also apparent at the level of 0.3 μg/ml, where, on average, there was less than 100 ng/ml of IgE produced following exposure to the gamma-1 version versus over 150 ng/ml of IgE produced following exposure to the gamma-4 antibody. Furthermore, the gamma-1 version completely inhibited IgE production at half the concentration of the original primate antibody. These results are further substantiated by the discussion in Example 3 on page 73, where it is disclosed that neither the primate nor the gamma-4 version of 6G5 inhibited IgE production in vivo, whereas the gamma-1 version had a significant effect (see Figures 9 and 10, and especially the second panel of Figure 10).

Regarding the 5E8 antibody, applicants respectfully disagree with the Examiner's analysis of the data in Figure 3. In contrast to what the Examiner states, the results from the gamma-1 versus the gamma-4 version are not comparable, because the gamma-1 version clearly inhibited IgE production to a greater extent than the gamma-4 version. For instance, at the lowest concentration tested, the gamma-1 version inhibited on average 50% of the control level of IgE production whereas the gamma-4 antibody had no effect. This interpretation is further substantiated by the data presented in Figure 4, and by the discussion at page 69, lines 12-18, where the statistical significance of the results of Figure 3 is presented.

Thus, the present inventors have surprisingly discovered that the human gamma-1 containing antibodies of the present invention possess substantially better activity than an otherwise identical version containing a gamma-4 human constant region domain. The gamma-1 version was shown to inhibit IL-4 induced IgE production by B cells, both in vitro and in a SCID mouse model more effectively than the gamma-4 version. It would be reasonable to expect that gamma-3 antibodies would behave similarly to gamma-1 antibodies, given that they bind to the same Fc receptors as do gamma-1 antibodies. Moreover, the Fab_2 version containing the same variable regions was inactive (see page 73, lines 2-4). Therefore, the present inventors have surprisingly found that effector function is highly significant to the therapeutic properties of the subject anti-human CD23 antibodies.

In fact, in view of the inventor's initial expectations, based on previous literature which suggested that Fc effector function was not necessary for induced IgE inhibition, human gamma-4 versions of the antibodies were initially produced. However, as discussed at page 17 of the application, it was surprisingly found that gamma-4 versions produced from

the primate antibodies were relatively ineffective, i.e., they required significantly higher concentrations than the primate versions in order to inhibit IL-4 induced IgE production in vitro assays. Thereafter, it was surprisingly found that, when these same antibodies were converted to gamma-1 antibodies, i.e., by substitution of the primate constant domains with human gamma-1 constant domains, that they very effectively inhibited IL-4 induced IgE production in vitro.

Thus, the present application contains convincing evidence as to the unexpected significance of the human gamma-1 constant domain on activity, which is not fairly suggested by the prior art. Indeed, the reasonable expectation prior to the present invention would have been that the incorporation of any particular human constant domain would have little or no effect on IgE inhibitory activity, and that the only potential benefit would be reduced immunogenicity relative to the original intact antibody.

Bonnefoy does not teach an antibody having either gamma-1 or gamma-3 human constant domains that inhibits IgE production to a higher extent than the original antibody. Thus, if Bonnefoy is appropriately taken as, at most, a §103(a) reference, then the surprising and unexpected results reported in the specification should be considered as probative of non-obviousness. The existence of novel or superior unexpected properties, undisclosed by the prior art, weighs heavily in favor of a conclusion that the claimed composition is not obvious. In re Albrecht, 514 F.2d 1389, 1394-95, 185 USPQ 585, 588-90 (CCPA 1975); In re Blondel, 499 F.2d 1311, 182 USPQ 294 (CCPA 1974); In re Lunsford, 357 F.2d 380, 384-85, 148 USPQ 716, 719-21 (CCPA 1966); In re May, 574 F.2d 1082, 1092-94, 197 USPQ 601, 608-11 (CCPA 1978); Eli Lilly & Co., 630 F.2d at 126-33, 207 USPQ at 725-32. And where the prior art teaches away from the claimed invention, that is highly probative evidence that the invention is nonobvious. United States v. Adams, 383 U.S. 39, 148 USPQ 479 (1966); In re Mercier, 515 F.2d 1161, 1165-66, 185 USPQ 774, 777-79 (CCPA 1975); In re Rosenberger, 386 F.2d 1015, 1018 (CCPA 1967); American Original Corp. v. Jenkins Food Corp., 696 F.2d 1053, 216 USPQ 945 (4th Cir. 1982). By teaching that antibodies having gamma-4 domains, for instance, are just as useful as the original intact antibody for inhibiting IgE production, Bonnefoy in fact teaches away from choosing gamma-1 or gamma-3 domains as required by the present invention.

In view of the amendment to claim 1 above and the points raised herein, reconsideration and withdrawal of Bonnefoy as either a §102 or §103 reference is respectfully requested.

Next, claims 1, 2, 4-11 and 14-24 remain rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Queen (U.S. Patent 5,585,089) in view of Saxon et al. This rejection remains because the Examiner questions the unexpected nature of the results reported in the specification, and therefore does not give them appropriate consideration as evidence that is probative of non-obviousness. Applicants respectfully request reconsideration of the results reported in the specification in light of the above comments.

The Examiner also indicates that she does not understand why this rejection is directly inconsistent with the issuance of the '138 patent. Applicants respectfully submit that the rejection is inconsistent with the issuance of the '138 patent, because these references were considered and dismissed as irrelevant during the prosecution of the parent application (see the face of the '138 patent). Furthermore, the Examiner of the '138 patent did indeed vacate all prior art rejections in view of the unexpected results presented in the specification (see the Reply submitted on October 14, 1998 during prosecution of the '138 patent, a copy of which is attached hereto). Thus, by questioning the results reported in the specification and making rejections based on prior art considered and dismissed during prosecution of the parent application, the Examiner is in effect challenging the validity of an issued patent. Again, the claims at issue here are substantially the same as those in the '138 patent except for the inclusion of gamma-3 anti-human CD23 antibodies.

Reconsideration and withdrawal of the rejection based on Queen in view of Saxon is respectfully requested.

Claim 16 was rejected under 35 U.S.C. §112, second paragraph for indefiniteness because it depends on claim 3, which was previously canceled. This rejection is rendered moot by the cancellation of claim 16 above.

Finally, claims 1, 2, 5-9, 14, 15 and 17-22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Newman et al. (U.S. Patent 5,658,570) in view of Saxon et al. In the Examiner's opinion, although Newman does not disclose an anti-CD23 antibody having a gamma-1 constant region, it would have been prima facie obvious to substitute the gamma-1 region used in the anti-CD4 antibody also disclosed in Newman. Further, such antibodies would allegedly inhibit IgE production as taught by Saxon. Applicants respectfully traverse the rejection.

Applicants respectfully submit that there is no motivation provided in Newman to choose gamma-1 constant domains over any other gamma constant region or any other antibody isotype for that matter. Indeed, Newman does not even disclose that anti-CD23

antibodies are useful for inhibiting IgE production, let alone that antibody effector function plays a significant role in that activity. Although Saxon might teach that anti-CD23 antibodies are useful for inhibiting IgE production, Saxon does not make up for the lack of guidance in Newman to choose gamma-1 or gamma-3 antibodies in particularly.

Again, the existence of novel or superior unexpected properties, undisclosed by the prior art, weighs heavily in favor of a conclusion that the claimed composition is not obvious. In re Albrecht, 514 F.2d 1389, 1394-95, 185 USPQ 585, 588-90 (CCPA 1975); In re Blondel, 499 F.2d 1311, 182 USPQ 294 (CCPA 1974); In re Lunsford, 357 F.2d 380, 384-85, 148 USPQ 716, 719-21 (CCPA 1966); In re May, 574 F.2d 1082, 1092-94, 197 USPQ 601, 608-11 (CCPA 1978); Eli Lilly & Co., 630 F.2d at 126-33, 207 USPQ at 725-32. Applicants have surprisingly found that gamma-1 antibodies are substantially better at inhibiting IgE production than are gamma-4 antibodies, thereby teaching for the first time that effector function is important for anti-CD23 antibody therapeutics. It is reasonable to predict that gamma-3 antibodies would have the same utility, given that gamma-3 antibodies bind to the same Fc receptors as gamma-1 antibodies. Neither Newman nor Saxon provides any motivation to choose gamma-1 or gamma-3 constant domains over any other isotype. Therefore, these references do not render obvious the claimed invention.

Although Newman was not cited during prosecution of the '138 patent, applicants respectfully note that this rejection still implicitly challenges the validity of the '138 patent, seeing as the present claim are substantially the same as the issued claims except for the inclusion of gamma-3 antibodies. The Examiner cites Newman as rendering obvious gamma-1 antibodies, not gamma-3 antibodies. Therefore, if this rejection is maintained, particularly in view of the amendments above, the Examiner is in effect challenging the validity of an issued U.S. patent. Indeed, the Federal Circuit has held that "even if prior art is more pertinent than art which patent examiner cited, this fact alone does not rebut statutory presumption of validity." Seattle Box Company, Inc. v. Industrial Crating & Packing, Inc. et al., 221 USPQ 568 (Fed. Cir. 1984). Reconsideration and withdrawal is respectfully requested.

All issues raised by the Office Action dated April 23, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned **"Version with markings to show changes made"**.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

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Enclosure: Appendix
Copy of October 14, 1998 Reply

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claim 1 was amended as follows:

1. (Twice Amended) An anti-human CD23 monoclonal antibody comprising human constant regions that bind to human Fc receptors [which] wherein said constant regions are selected from [a] human gamma-1 or human gamma-3 monoclonal antibody constant domains, [which] wherein said antibody inhibits IL-4 induced IgE expression by B-cells in vitro to a greater extent than the anti-human CD23 monoclonal antibody which lacks a human gamma-1 or gamma-3 constant region.

Patent
Attorney's Docket No. 012712-353

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Mitchell E. REFF et al	)	
	)	
Application No.: 08/803,085	)	Group Art Unit: 1642
	)	
Filed: February 20, 1997	)	Examiner: J. Reeves
	)	
For: GAMMA-1 ANTI-HUMAN CD23 MONOCLONAL ANTIBODIES AND USE THEREOF AS THERAPEUTICS	)	

REPLY AND AMENDMENTS PURSUANT TO 37 C.F.R. §§1.111, 1.115 AND 1.119

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action [non-final rejection] mailed April 14, 1998, kindly amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 15, last line, change "commonly assigned Application Serial No. 08/379,072 (now allowed)" to --U.S. Patent No. 5,658,570--.

Page 16, last line, change "commonly assigned Application Serial No. 08/379,072 (now allowed)" to --U.S. Patent No.5,658,570--.

Page 20, fifth line from the bottom, change "U.S. Serial No. 08/147,696 (now allowed)" to --U.S. Patent No.5,648,267--.

Page 21, line 14, change "U.S. Serial No. 08/488,376" to --5,811,524--..

Page 22, first line, change "Serial No. 08/379,072" to --U.S. Patent No. 5,658,570--.

Page 31, line 11, change "Histopaque" to --HISTOPAQUE--.

Page 41, line 5, change "Cricket Graph" to --CRICKET GRAPH--.

Page 48, penultimate line, change "Epicurian Coli® XL1-Blue" to --EPICURIAN COLI XL1-BLUE®--.

Page 49, line 14, change "Wizard" to --WIZARD--.

IN THE CLAIMS:

Kindly amend Claims 1, 9-11, and 38-41 as set forth below.

1. (Twice amended) An anti-human CD23 monoclonal antibody that binds human CD23, wherein said monoclonal antibody inhibits IL-4 induced IgE expression by B-cells *in vitro* and [comprising] comprises a human gamma-1 constant region.

9. (Amended) The anti-human CD23 monoclonal antibody of Claim 1, having a CD23 binding affinity ranging from 0.01nM to 1000nM.

10. (Amended) The anti-human CD23 monoclonal antibody of Claim 9, having a CD23 binding affinity [of at least] ranging from 5nM to 1000nM.

11. (Amended) The anti-human CD23 monoclonal antibody of Claim 9, having a CD23 binding affinity [of at least] ranging from 100nM to 1000nM.

38. (Amended) The anti-human CD23 monoclonal antibody of Claim 1 wherein the variable domains are [derived] from a monoclonal antibody having light chain and heavy chain variable domains with sequences SEQ ID NO: 3 and SEQ ID NO: 4, respectively.

39. (Amended) The anti-human CD23 monoclonal antibody of Claim 1, wherein the variable domains are [derived] from a monoclonal antibody having light chain and

heavy chain variable domains with sequences SED ID NO:1 and SEQ ID NO:2, respectively.

Claim 40, line 1, after "CD23" insert --monoclonal--.

Claim 41, line 1, after "CD23" insert --monoclonal--.

Kindly cancel non-elected Claims 26-37.

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, Claims 1, 9, 10, 11, 38, 39, 40 and 41 are amended in order to expedite prosecution. All of the Claim amendments find support in the original claims et. seq. Further, the specification has been amended to cure certain informalities. Finally, the non-elected Claims have been canceled in order to expedite prosecution.

Turning now to the Office Action, Applicants acknowledge the previous election with traverse of Claims 1-25, which are directed to anti-human CD23 monoclonal antibodies. Previously submitted Claims 38-41 correspond to the elected subject matter

as they likewise are directed to anti-human CD23 monoclonal antibodies. As noted above, in order to expedite prosecution, non-elected Claims 26-37 are canceled herein. Therefore, the Restriction Requirement is now moot. As a result of the amendments to date, Claims 1-11, 14-24 and 38-41 remain pending, and all are directed to the elected subject matter.

Applicants next note with appreciation that the previous Reply was successful to the extent that the prior rejections have all been withdrawn. However, the Claims stand newly rejected, and the Specification stand objected to based on new objections and rejections. The specific issues are addressed below. To the extent possible, these issues are addressed in the order that they are raised in the Office Action.

First, the Specification stands objected to as not containing an Abstract. This objection is cured as an Abstract on a separate page accompanies this Reply.

The objection to the disclosure for failing to identify the current status of earlier commonly assigned applications is rendered moot by the present amendments.

The objection to Figures 2, 8, 9 and 10 is noted. The Examiner is respectfully requested to hold this objection in abeyance until this application is in condition for allowance. Formal figures and any amendments to the specification necessitated thereby will be filed with payment of the Issue Fee, as provided by the Rules.

The objection to the trademark terms contained in the specification is also noted. All of these phrases are now capitalized in accordance with the rules.

Thus, based on the foregoing, withdrawal of the objections to the specification is respectfully requested.

Claims 1-11, 14-24 and 38-41 stand rejected under 35 U.S.C. §112, second paragraph, as assertedly being indefinite. This rejection is addressed below for completeness. However, it is anticipated that this rejection should be moot based on the Claim amendments made herein.

First, the Claims are asserted as being indefinite with respect to the description of the binding affinity of the subject monoclonal antibody. This rejection should be moot as Claim 1 has been amended, in accordance with the Examiner's suggestion, to recite that the antibody binds human CD23.

Claims 1-6, 8-11, 14-19, 22-24 and 38-41 are also asserted as being indefinite in the recitation "inhibits IgE expression". While it is believed that the meaning of "inhibits IgE expression" would be clear to one of ordinary skill, in order to expedite prosecution, Claim 1 has been amended as suggested by the Examiner, namely to recite that the antibody inhibits IgE expression by B-cells *in vitro*. Therefore, based on the fact that Applicants have adopted the Examiner's suggestion, this Claim should now be definite.

Claims 9 and 22 are asserted to be indefinite in the recitation "having a binding affinity". This rejection is moot as Claim 9 now instead recites "CD23 binding affinity", as also suggested by the Examiner.

Claims 38-41 are also asserted to lack proper antecedent basis for the recited "anti-human CD23 antibody". This rejection should be moot as Claims 38-41 have been amended to clarify that the antibody is a monoclonal antibody.

Finally, Claims 38 and 39 are asserted to be unclear as to the intent of "derived" in the context of variable regions. More specifically, the Examiner queries whether modifications of such variable regions are intended. This criticism is moot as "derived" has been deleted in accordance with the Examiner's suggestion.

Thus, based on the foregoing, withdrawal of the §112, second paragraph, rejection of Claims 1-6, 8-11, 14 and 19, 22-24, and 38-31, is respectfully requested.

Claims 10-11 and 23-24 also stand rejected under 35 U.S.C. §112, second paragraph, based on the recitation of "at least" with respect to antigen binding affinity. This rejection, while believed to be clearly improper, has been rendered moot by the deletion of "at least" from Claims 10-11, and substituting the preferred antigen binding affinity ranges in said Claims. Withdrawal of this rejection is respectfully requested.

Claims 1-6, 8-11, 14-24, and 38-41 also stand rejected under 35 U.S.C. §112, first paragraph, as assertedly not being adequately enabled by the teachings of the subject application. The Office Action indicates that the disclosure only enables a human gamma-1 constant region containing anti-human CD23 monoclonal antibody that inhibits Il-4 induced IgE expression by B-cells *in vitro*, or in a human SCID mouse model. Apparently,

the Examiner is of the opinion that the Specification does not sufficiently demonstrate that the subject monoclonal antibodies will possess therapeutic activity.

However, with respect to this rejection, it is noted at the outset that the antibody claims now provide expressly that the subject monoclonal antibody inhibits IL-4 induced expression by B-cells *in vitro*. Therefore, at the least with respect to the antibody claims (the pharmaceutical composition claims will be addressed infra), the Claims are directed to subject matter which the Examiner expressly indicates at paragraph 14 of the Office Action are enabled. Therefore, at the least, withdrawal of the §112 enablement rejection of Claims 1-6, 8-11, and 38-41, which are directed to an anti-human CD23 antibody, is respectfully believed to be in order.

With respect to the antibody Claims, Applicants respectfully acknowledge that the preferred application of the subject antibody is as a therapeutic agent. In particular, as properly noted by the Examiner, these antibodies desirably will be used for treating inflammatory conditions, allergic disorders, or autoimmune diseases. However, this is not the only application of an anti-CD23 antibody disclosed in the subject application or the only application which would be known to one of ordinary skill based on the teachings of this application and what is known in the CD23 antibody art. Indeed, as stated at page 3 of the subject application, anti-CD23 antibodies are also useful as diagnostic agents, for example for assaying the presence of IgE receptors on cell types. Therefore, unlike the pharmaceutical composition claims, the enablement of the subject monoclonal antibodies

does not hinge on their ultimate usage as therapeutics, notwithstanding the fact that this is clearly the preferred and intended application thereof. In fact, these antibodies possess alternative utility as diagnostic agents.

Also, with respect to the pharmaceutical composition claims, Applicants respectfully submit that they would be willing to delete the recitation "pharmaceutical" and simply claim a composition containing the subject antibody if necessary and if this would render the enablement rejection moot. While Applicants respectfully submit that the subject antibodies do possess therapeutic capability, and that this is sufficiently demonstrated based on the *in vitro* and *in vivo* evidence already provided, in order to expedite prosecution, Applicants would delete "pharmaceutical" from the composition claims, if this would render the enablement rejection moot.

Turning now to the Examiner's basis for the enablement rejection as it pertains to the current pharmaceutical composition claims, the position of the Examiner apparently is that "the specification has not provided a link between inhibition of IgE expression in the SCID mouse model and the treatment of allergic diseases, autoimmune diseases, or inflammation." With respect to the position taken by the Examiner, it is respectfully noted at the outset that it is only necessary to demonstrate a single pharmaceutical usage enabled by the teachings of the application (which would fall within the scope of the disclosure).

It is not necessary for enablement that Applicants demonstrate that the subject antibodies will be useful for treating all of the recited conditions, i.e., allergic diseases,

asthma, autoimmune diseases, or inflammation. This is not necessary, as the pharmaceutical methods are not currently under examination. Rather, the Claims under examination are directed generally to a pharmaceutical composition comprising an anti-CD23 antibody. Therefore, in order to satisfy the enablement requirement, it is only necessary to establish that it is reasonable to conclude, based on the information contained in the subject application and what is known in the art, that such antibodies will be useful for some pharmaceutical usage. Accordingly, based on the subject disclosure, it is only necessary to establish that the subject anti-human CD23 antibodies containing a human gamma 1 constant region, will be useful in treating some allergic disease, asthma, autoimmune disease or an inflammatory disease. This will be established *infra*.

As to the enablement rejection, one apparent concern of the Examiner is that the data obtained in SCID mice may not correlate to human efficacy. With respect to this issue, it is respectfully noted that many functional studies involving monoclonal antibodies in mice have correlated well to clinical studies in humans. Examples wherein mouse data has been extrapolated to human clinical trials include monoclonal antibodies to CD3, monoclonal antibodies to CD4, and monoclonal antibodies to TNF factor. In all of these cases, functional effects seen in animal models have correlated into similar functional effects in humans. Therefore, Applicants respectfully submit it is reasonable to assume, absent evidence to the contrary, that the information obtained in the SCID mouse model should correlate to human clinical efficacy.

Moreover, in the particular case of antibodies that inhibit IgE as claimed herein, published clinical trials involving a monoclonal antibody to IgE, which blocks the effects mediated by IgE, indicate that this antibody is efficacious in the treatment of allergic conditions, i.e., allergic rhinitis and allergic asthma. For example, Fahy et al., *Journal of Allergy Clinical Immunology*, January 1996, describes, in human clinical trials, the effective treatment with a monoclonal antibody directed against IgE on allergic airway responses in asthmatic subjects. The authors conclude, based on the results, the following:

> "treatment with a monoclonal antibody directed against the Fc portion of IgE reduces circulating IgE and inhibits the early and late responses to inhaled allergen in allergic asthmatic subjects. Targeting IgE with [the exemplified antibody] might be a useful treatment for allergic asthma".

Therefore, the authors concluded that an antibody which inhibits IgE provides a suitable therapeutic for treating an allergic condition, namely allergic asthma. Moreover, Fahy et al., *American Journal of Respiratory Critical Care Medicine*, Vol. 155, pages 1828-1834, 1997, and Boulet et al., *American Journal of Respiratory Critical Care Medicine*, Vol. 155, pages 1835-1844, 1997, similarly studied the effects of an anti-IgE monoclonal antibody in human asthmatic subjects. The authors conclude, based on their obtained results, that:

> "treatment of allergic asthmatic subjects with an anti-IgE antibody significantly reduces serum IgE concentrations and attenuates both the early- and late-based response to alert allergen challenge. This finding establishes the involvement of IgE in the pathophysiology of both the early- and late-phase

> responses to allergen and inhalation and suggests a novel potential treatment for allergic asthma".

(Fahy, *American Journal Respiratory Critical Care Medicine*, Vol. 155, page 1833, 1997). Also, Boulet et al. (*Id.*) concluded based on their results using the same antibody administered to human patients having allergen induced early asthmatic responses to the following "in conclusion [the exemplified antibody] is a powerful suppressor of allergen-induced type 1 (an anaphylactic) responses in the airway". The studies provide a rationale for designing investigations of efficacy of the antibody is a therapy of allergic asthma.

Accordingly, all of these references provide evidence in humans that an allergic condition can be effectively treated by blocking the effects mediated by IgE by administration of an immunotherapeutic antibody that inhibits IgE activity. Still further, Casale et al teach administration of an anti-IgE humanized monoclonal antibody to patients having ragweed-induced allergic rhinitis. (Casale et al., *Journal of Allergy Clinical Immunology*, Vol. 100, No. 1, pages 110-120.) They similarly concluded, based on the results, that: "Our data suggests that if sufficient quantities of [exemplified humanized antibodies] are given to fully suppress serum free IgE levels then allergic rhinitis systems will likely decrease or be ameliorated". Therefore, there is human clinical evidence substantiating the efficacy of antibodies that inhibit IgE for effective treatment of two different allergic disease conditions. Therefore, based on the foregoing, it is reasonable to conclude that the subject antibodies should possess similar therapeutic efficacy, especially

given their enhanced effector activity (based on the presence of a human gamma-1 constant region). Moreover, the results reported in human clinical trials substantiate Applicants arguments that it is reasonable to conclude that the observed *in vitro* activity and *in vivo* data obtained in a SCID mouse model should correlate to human clinical efficacy.

As further evidence of pharmaceutical efficacy, it is additionally noted that other researchers have reported that anti-CD23 antibodies are effective in other (non-SCID) animal models of allergic asthma. For example, a monoclonal anti-murine CD23 (B3B4) has been demonstrated to block long eosinophil infiltration in a mouse. (Coyle et al, *Journal of Experimental Medicine*, Vol. 183, April 1996, pages 1303-1310.) It is further noted that the monoclonal antibody disclosed in the reference blocks the binding of IgE complexes to CD23 as does the primatized monoclonal anti-human CD23 antibodies disclosed in the subject application. (*See* Figure 7 of the subject application). Therefore, based on a similar blocking activity of the subject antibodies, it is further reasonable to assume that it should possess similar therapeutic efficacy for the treatment of human allergic diseases.

Also, in express rebuttal of the Examiner's query as to the correlation between IgE expression and allergic conditions, Applicants note that allergic specific IgE has been found to correlate with eosinophil migration into the lung in allergic asthma subjects. (*See* Peebles et al., *Journal of Allergy Clinical Immunology*, Volume 101, No. 2, pages 265-273 (1998)). Accordingly, it is reasonable to expect that reduction of allergen specific IgE by

administration of a monoclonal anti-human CD23 as claimed herein will inhibit eosinophil infiltration in human asthma, and therefore mediate a therapeutic benefit.

Still further, it has been shown that an allergen specific IgE also correlates with the symptoms of perineal or allergic rhinitis. See, for example (Ohashi et al, *Scandinavian Journal of Immunology*, line 46, pages 67-77 (1997); Ohashi et al, *Anals of Allergy, Asthma and Immunology*, Vol. 79, pages 213-220 (1997); Ohashi et al, *Scandinavian Journal of Immunology*, Vol. 47, pages 167-178 (1998); and Pullerits et al, *J. Allergy Clin Immunol*, 100:601-605 (1997). More specifically, these references teach that the allergic symptoms in this particular disease are mediated by basophil degranulation, which is caused by the binding of allergen to allergen specific IgE, which is bound to the surface of basophils by high affinity receptor for IgE. Consequently, blocking the production of IL4-induced IgE production by B-cells, by the administration of a monoclonal anti-human CD23 antibody, such as described and claimed in the present invention, would be expected to lower the level of allergen-specific IgE, thereby resulting in a decline of allergen-specific IgE coated basophils. This would be expected, moreover, to moderate the symptoms of allergic rhinitis, an allergic disease within the scope of the disclosure.

Moreover, in the particular case of inflammatory diseases, it has been reported that a monoclonal anti-murine CD23 antibody (B3B4) blocks the establishment of collagen induced arthritis in mice. (Plater-Zyberk et al, *Nature Medicine*, Volume 1, No. 8, August 1995). The reference teaches marked amelioration of established collagen-induced arthritis

by treatment with antibodies to CD23 *in vivo*. Moreover, the authors note that their findings demonstrate "the involvement of CD23 in a mouse model of human rheumatoid arthritis". Thus, it is further clear from the reference that this data was obtained in an art-recognized mouse model for a human inflammatory condition, i.e., rheumatoid arthritis.

It is hypothesized by an inventor if this application that the effect of the anti-CD23 antibody in this mouse model is probably attributable to blocking of the pro-inflammatory effects of soluble CD23. With respect thereto, the monoclonal anti-human CD23 antibodies disclosed in this application have been found to bind to soluble CD23. Consequently, it is reasonable to expect that these antibodies will similarly block the pro-inflammatory effects of soluble CD23, and thereby inhibit inflammatory responses.

Accordingly, based on the foregoing, there is substantial evidence in the literature which substantiates the accepted therapeutic efficacy of antibodies that inhibit IgEs for treating human allergic and autoimmune diseases, and therefore why it is reasonable to assume that the data in this application will correlate to successful human therapy.

As another basis of the enablement rejection, the Examiner further suggests that selecting an antibody having immunotherapeutic activity is unpredictable as it must possess sufficient specificity and affinity towards the antigen target to be immunotherapeutically useful. The Office Action further indicates that the specification is silent concerning what type of specificity and affinity would be necessary for the subject antibodies to be therapeutically useful. However, it should be noted that the subject application discloses

affinity ranges, some of which are recited in dependent claims. Moreover, the apparent affinity of the exemplified anti-human CD23 primate and primatized monoclonal antibodies, i.e., 5E8 and p5E8G1, have been measured by Scatchard analysis, and are contained in this application. These affinities are less than 1nM. (These results contained in Figure 4.)

With respect thereto, it should be noted that these affinities are equivalent to those which have been demonstrated to be effective for previous immunotherapeutic antibodies. For example, RITUXAN®, an anti-CD20 antibody (developed by IDEC Pharmaceuticals Corporation) which was recently approved by the FDA for treating B-cell lymphoma, has a similar affinity to its target antigen. (*See* Reff et al, *Blood*, Vol. 83, No. 2, 1994, pages 435-445 (1994)).

Moreover, Applicants respectfully submit that the selection of an appropriate antigen binding affinity for therapeutic efficacy would be well within the level of ordinary skill in the art. Also, it should be noted that the specificity of the subject antibody (p5E8G1) has been measured on a panel of 34 human tissues. The subject antibody does not bind to any tissues except those containing B-lymphocytes (MPASS Incorporated). Therefore, the subject antibody is highly specific for CD23.

As another basis to the rejection, the Examiner further indicates that immunotherapy and *in vivo* inhibition of cytokine-mediated IgE expression is a complex and unpredictable art. In support thereof, she cites Kohl et al, *Fundamental Immunology*, 3rd Edition, Chapter

21, which teaches the complex interaction of cytokines. This reference has been considered. While it is acknowledged that the use of antibodies as therapeutic agents can be unpredictable, as is the effect of cytokines, the predictability of the subject invention has been established. Indeed, Applicants respectfully submit that relevant evidence substantiating the efficacy of anti-CD23 antibodies are contained in the afore-described references (attached to this Response), which demonstrate convincingly the accepted therapeutic efficacy of antibodies that inhibit IgE (inflammatory and allergic conditions) for treatment of human diseases. Therefore, based thereon, it is reasonable to conclude that the results obtained in the SCID mouse model should correlate to effective human therapy.

As discussed above, it is not necessary that Applicants demonstrate that the subject antibody will possess efficacy in treatment of all allergic autoimmune diseases or inflammatory conditions. Rather, Applicants must merely demonstrate, based on the information contained in the subject application and what is generally known in the art, that it is reasonable to assume that the subject anti-human CD23 monoclonal antibodies will possess a pharmaceutical efficacy within the scope of the disclosure. This is reasonable to conclude based on the references discussed above, which provide evidence as to the efficacy of antibodies that inhibit IgE in human clinical studies and mouse models (which models correlate to human autoimmune and allergic conditions). Therefore, in contrast to the Office Action, the therapeutic efficacy of an anti-CD23 antibody to inhibit cytokine-induced IgE expression by B-cells is not unpredictable. To the contrary, the data in this

application and that of others, suggest that for human PBMCs which contain a mixture of human white blood cells, that human B-cells can be accessibly induced by IL-4 to produce IgE, and that such induction can be effectively blocked by an anti-CD23 monoclonal antibody.

The Examiner's criticism in item H of the Office Action with respect to IgE expression (what is inhibited) is moot. As discussed above, the Claims have been limited to monoclonal antibodies which are capable of inhibiting IL4-induced IgE expression by B-cells.

The Office Action also alleges that the unpredictability of immunotherapeutics in general is evidenced by the Seaver and Paul references. These references have been considered, as well as the Delespesse et al, Vercelli et al, and Haak-Frendscho et al references cited by the Examiner. Essentially, all of these references are relied upon to establish the "art recognized complexity of treating immune systems disorders". As discussed above, while Applicants acknowledge that there does exist some predictability in isolating and identifying an antibody to an unknown target, which possesses immunotherapeutic activity, Applicants respectfully submit that this unpredictability has been adequately rebutted based on the above-discussed references which support the human clinical efficacy of anti-human CD23 antibodies. Accordingly, in weighing the factors which are properly considered in determining whether practice of an invention

would require undue experimentation, the weight of the analysis does not clearly favor a finding of undue experimentation.

Moreover, with respect to the enablement rejection, and as discussed above, it would appear that this rejection can potentially be obviated by deleting the term "pharmaceutical" from Claims 14 to 24, as suggested by the Examiner. With respect thereto, Applicants would prefer, if at all possible, to retain the recitation in the Claims that the composition functions as a pharmaceutical agent, as this is reasonable to conclude based on the evidence provided. However, as discussed above, if deletion of this phrase would render the rejection moot and the Examiner is otherwise prepared to allow the application, Applicants would be willing to limit Claims 14-24 as suggested in order to expedite prosecution.

Accordingly, based on the foregoing, withdrawal of the §112 enablement rejection in its entirety is respectfully requested. Essentially, based on the information of record and that provided herein, there exists substantial evidence which would allow one skilled in the art to reasonably conclude that the subject anti-human CD23 monoclonal antibody, which comprises a human gamma 1 constant domain, will provide a suitable therapeutic agent for treatment of human diseases including allergic and inflammatory conditions.

Claims 1-2, 4-11, 14-15, 17-24 and 40-41 further stand rejected as allegedly being rendered unpatentable based on prior art. This rejection is respectfully traversed. In particular, the Examiner asserts that these claims are unpatentable over the combination

of Bonnefoy et al as evidenced by Pene et al taken in combination with Flores-Romo et al and Presta et al.

With respect thereto, the Examiner relies upon Bonnefoy based on its disclosure that CD23 is the low affinity receptor for IgE found on B-lymphocytes. Moreover, the references are further relied upon based on the disclosure that antibody specific for human CD23 was known and available at the time the invention was made. Also, Pene et al is relied upon to substantiate that the monoclonal antibody exemplified by Bonnefoy (IEMAB25) has the ability to inhibit IL4-induced IgE expression by B-cells, like the subject antibodies. Further, Flores-Romo is relied upon based on its disclosure that monoclonal antibodies might be able to inhibit IgE expression *in vivo* based on the fact that *in vivo* administration of rabbit polyclonal antisera specific to human CD23 inhibited IgE synthesis *in vitro*. The Examiner concludes, based thereon, that the combined teachings of Bonnefoy, Pene et al and Flores-Romo would suggest the therapeutic efficacy of monoclonal antibodies specific for human CD23 having affinities and functional properties falling within the claimed ranges. With respect thereto, the Examiner properly notes that none of these references teaches or suggests a monoclonal antibody which comprises a human gamma 1 constant region as recited in Claim 1. It is alleged in the Office Action that this deficiency is cured by Presta. However, the position of the Examiner is respectfully but strenuously traversed.

As properly recognized by the Examiner, Presta et al teaches humanization of an antibody directed against IgE. The reference reports humanization of such antibody because antibodies to IgE are useful for blocking the binding of IgE to its receptor and are therapeutically useful in the treatment of allergy. More specifically, the reference studies the effect of mutation on a humanized antibody reported therein in order to determine what specific framework residues affect antigen binding and to determine which particular residues in the CDR interact with IgE.

However, contrary to the Office Action, Applicants respectfully submit that this reference would not fairly teach or suggest the subject invention. This is because Presta et al contains no disclosure which would indicate to one skilled in the art the potential benefit of the incorporation of a human gamma 1 constant domain on the ability of a particular antibody to human CD23 to inhibit IgE production. At best, Presta et al would merely suggest that it would have been *prima facie* obvious to make chimeric antibodies from a murine antibody that inhibits IgE in order to reduce the immunogenicity thereof upon therapeutic administration. However, the reference would contain no suggestion as to which particular human constant domain to select, or any enhanced effect thereof on therapeutic activity. Moreover, based on what was known in the art relating to anti-CD23 antibodies, it would have been reasonably predicted that the particular constant domain would have little or no effect on activity. In this regard, and as disclosed in this application, it had been previously reported that a Fab_2, i.e., which lacks a constant region,

is just as potent in inhibiting IgE production as a complete antibody. Thus, available information prior to the present invention would have suggested to one of ordinary skill that effector function was not significant to IgE inhibitory activity of anti-CD23 antibodies. In fact, this is supported by the Flores-Roma reference cited in the rejection. As discussed at page 4 of the subject application, the authors of Flores-Romo et al report that Fab_2 prepared from anti-CD23 antibodies inhibit antigen-specific IgE responses *in vivo* comparable to intact antibodies.

Thus, at best, Presta et al would arguably suggest that the substitution of a human constant domain in favor of a murine constant domain in a murine antibody that inhibits IgE could result in an antibody having less immunogenicity when administered to humans. However, the references, separately or in combination, would not fairly suggest that any particular human constant domain in an anti-human CD23 antibody would have any significant effects on IgE inhibitory activity, especially based on the fact that a Fab fragment, i.e., which does not contain any constant domain, had been reported to be equally potent as a complete anti-human CD23 antibody.

By contrast, the present inventors have surprisingly discovered that the human gamma 1 containing anti-human CD23 antibodies of the present invention possess substantially better activity than an otherwise identical anti-human CD23 antibody containing a human gamma 4 constant domain. More specifically, as discussed in the application, the gamma 1 version inhibited IL4-induced IgE production by B-cells, both

in vitro and in a SCID mouse model much more effectively than the gamma 4 version. Moreover, the Fab_2 version containing the same variable regions was inactive. Therefore, the present inventors have surprisingly discovered that effector function is apparently highly significant to the therapeutic properties of the subject anti-human CD23 antibodies.

In fact, in view of the inventors' initial expectation, based on the previous literature, which suggested that the Fc effector function was not necessary for induced IgE inhibition, human gamma 4 versions of a subject antibodies were initially produced. However, as discussed at page 17 of the application, it was surprisingly found that the gamma 4 versions (produced from both of these primate monoclonal antibodies) were relatively ineffective, i.e., they required significantly higher concentrations (relative to gamma 1 version) in order to inhibit IL4-induced IgE production in *in vitro* assays. Moreover, it was surprisingly found that, when these same antibodies were later converted to human gamma 1 versions, i.e., by substitution of the primate constant domains with human gamma 1 constant domains, that they very effectively inhibited induced IgE production *in vitro*.

Therefore, the subject application contains convincing evidence as to the unexpected significance of the human gamma 1 constant domain on activity, which is not fairly suggested by the prior art. Indeed, the reasonable expectation, prior to the present invention, would have been that the incorporation of any particular human constant domain would have little or no effect on IgE inhibitory activity, and that the only potential benefit would be reduced immunogenicity relative to an intact murine antibody. Accordingly,

based on these unexpected results which are not fairly suggested by the prior art, withdrawal of the §103 rejection based on Bonnefoy taken in view of Pene et al, Flores-Romo et al and Presta et al is respectfully requested.

Claims 1-4, 6-11, 14-17, 19-24 and 40-41 further stand rejected under 35 U.S.C. §103 as assertedly being obvious over the same references, i.e., Bonnefoy, Pene et al, Flores-Romo, taken in view of Strike et al, and Cruse et al. Bonnefoy, Pene et al, and Flores-Romo, which references have been discussed above.

For the reasons set forth therein, these references separately or in combination fail to teach or suggest the gamma 1 constant domain containing antibodies of the present invention, or the enhanced results obtained thereby. The addition of Strike et al, alone or in view of Cruse, does not cure the deficiencies of the rejection. Strike et al is cited based on its disclosure relating to methods for producing human antibodies. Essentially, the Examiner takes the position that it would have been obvious based on this disclosure to have produced an anti-human CD23 antibody according to the disclosed *in vitro* immunization procedure. The Office Action further indicates that while Strike et al do not classify their IgE antibodies by subclass, in view of Cruse, one skilled in the art would conclude that IgG1 antibodies specific for the CD23 antigen could be obtained by the disclosed method. However, the position of the Examiner is respectfully traversed.

Strike et al acknowledgedly discloses a technique to produce human hybridomas which secrete human antibodies to antigens. In particular, the reference reports this

technique for producing antibodies against foreign antigens, i.e., sheep erythrocytes. However, there is nothing in the reference which would teach or suggest the specific use of such methodology for producing human monoclonal antibodies to human CD23. Moreover, there is no indication that the disclosed in vitro technique would be successful. Also, there is reason to believe that it would not be.

In this regard, it should be noted that this methodology has never been recorded to be successful in producing high-infinity human antibodies to human antigens. Therefore, Strike et al would not fairly suggest the claimed antibodies, since it does not suggest the use of the disclosed methods to make anti-human CD23 antibodies, and also there would be no reasonable expectation that the disclosed method would be useful for producing a human antibody specific to human CD23.

Moreover, even assuming *arguendo* that this reference rendered the claims *prima facie* obvious, the rejection should properly be withdrawn based on the unexpected results achieved by the subject invention. For the same reasons set forth in the traversal of the previous §103 rejection, the prior art would not fairly suggest that the selection of any particular human constant domain would be instrumental on the activity of an antibody specific to human CD23. Quite surprisingly, it has been found that the human gamma 1 constant domain has a significant effect on IgE inhibitory activity, in contrast to an otherwise similar antibody which contained a gamma 4 constant domain. These results

would not have been fairly suggested based on the prior art, including Strike et al, taken alone or in view of Cruse et al.

To the contrary, even assuming *arguendo* that it could have been reasonably expected that an IgG1 anti-human CD23 antibody could have been produced according to the disclosed *in vitro* immunization technique, there would have been no reasonable expectation that it would possess any enhanced activity relative to antibodies containing other human constant domains. Accordingly, based on the unexpected results which are not suggested by the prior art, withdrawal of the separate §103 rejection of Claims 1-4, 6-11, 14-17, 19-24 and 40-41, based on Bonnefoy taken in view of Pene et al, Flores-Romo et al and Strike et al, and further in view of Cruse, is respectfully requested.

Finally, Claims 1-4, 6-11, 14-17, 19-24 and 40-41 further stand rejected under 35 U.S.C. §103 as being unpatentable over Bonnefoy et al as evidenced by Pene taken in view of Flores-Romo and Capon et al. All of the references have been discussed above with the exception of Capon et al. Capon relates to a fusion protein, which contains an Fc portion. More specifically, the reference is cited based on its disclosure of a human gamma-1 constant region containing fusion protein, and it disclosure that the incorporation of the IgG1 constant region increases the plasma half-life of the resultant fusion protein in rabbits. The reference is also cited based on its disclosure that the IgG1 constant region is a "molecule well designed to avoid the clearance mechanisms of the body". However, for the same reasons set forth above, Applicants respectfully maintain that it could not have

been reasonably predicted, nor was it obvious, to have specifically incorporated the human gamma 1 constant domain in an anti-human CD23 antibody as claimed. In particular, as discussed above, the fact that the IgG1 constant domain apparently may increase the plasma half-life of some fusion proteins would not reasonably suggest that it would have any effect on the inhibition of IL4-induced IgE production by an anti-human CD23 antibody. This discovery could not have been recently predicted especially based on the previous disclosure by Flores-Romo that a Fab fragment possessed substantially the same activity as an intact antibody. Rather, the reasonable expectation prior to the present invention would have been that the Fc portion of an anti-CD23 antibody was not significant with respect to the ability of an anti-human CD23 antibody to inhibit IL4-induced IgE production. Quite surprisingly, this has been found to be not the case. Instead, the incorporation of the human gamma 1 constant domain results in an anti-CD23 antibody which significantly better inhibits IL-4 induced IgE production relative to an antibody containing a different human constant domain, i.e., a human gamma 4 chimeric version containing the same variable regions. Therefore, for the same reasons, the §103 rejection of Claims 1-4, 6-11, 14-17, 19-24 and 40-41 based on Bonnefoy et al taken in view of Pene et al, Flores-Romo and Capon et al should be withdrawn.

In summary, all the prior art rejections should be withdrawn since the references separately or in combination fail to teach or suggest the particular selection of a human gamma 1 constant domain in a human anti-CD23 antibody or the enhanced results obtained

thereby relative to anti-human CD23 antibody containing other human constant regions, or lacking a constant region altogether.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this reply, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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